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(54) Title: PHARMACEUTICAL PREPARATION FOR PERCUTANEOUS ABSORBTION

(57) Abstract

A transdermal patch comprises a backing, an adhesive for applying the patch, and a liner which is released to apply the patch. The adhesive contains both aspirin and an isosorbide mononitrate to achieve both anti-anginal and platelet washing properties.

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"Pharmaceutical Preparation for Percutaneous Absorbtion"

The invention relates to a transdermal patch.

Isosorbide nitrates are dilators of arterial and venous smooth muscle. The dilation on the venous system maintains or increases coronary artery flow while simultaneously reducing the oxygen requirement of the heart muscle. Patients with coronary artery narrowing frequently suffer from angina pectoris. The ability of the isosorbide mono nitrates (isosorbide-5-nitrate and isosorbide-2-nitrate) to function as vasodilators, in the manner described above, has lead to their extensive use in the prophylaxis of angina pectoris.

Nitrates have been formulated in many different ways to provide clinical relief of angina. For example, glyceryl trinitrate has been formulated as a sublingual tablet, spray and as a transdermal patch. Modified-release oral preparations (tablets and capsules) have also been made using the longer-acting nitrates, isosorbide dinitrate and isosorbide mononitrate. However, to best knowledge, there are no commercially available transdermal products containing these longer-acting nitrates.

Aspirin alters the balance between TXA_2 which promotes aggregation and prostacyclin (PGI_2) which inhibits it. Aspirin inactivates cyclo-oxygenase, acting mainly by irreversibly acetylating the active site on the enzyme, COX-1. This reduces both TXA_2 synthesis in platelets and prostacyclin synthesis in endothelium. Vascular endothelial cells can synthesise new enzymes whereas platelets cannot. After administration of Aspirin, TXA_2 synthesis does not recover until the affected cohort of platelets is replaced. This process typically takes 7 - 10 days. Also, inhibition of the cyclo-oxygenase of the

vascular endothelium requires higher concentrations of aspirin than does platelet cyclo-oxygenase. Therefore low doses of aspirin decrease the synthesis of thromboxane A_2 without drastically reducing prostacyclin synthesis. Clinical trials have now demonstrated the efficacy of aspirin treatment regimes for acute myocardial infarction, in reducing the incidence of reinfarction following recovery and in preventing occlusive vascular disease in individuals at particular risk.

Thus, it is now generally accepted that low-dose acetylsalicyclic acid (aspirin) can be beneficial as an anti-platelet agent. However, the oral delivery of aspirin may cause mucosal irritation, and bleeding, in susceptible individuals. Therefore, an alternative route of administration for aspirin would obviate these unwanted gastrointestinal side-effects.

According to the invention there is provided a transdermal patch comprising :-

a backing;

an adhesive for applying the patch; and

a liner which is released to apply the patch,

characterised in that

the adhesive contains a pharmaceutical product having anti-anginal and platelet washing properties.

In one aspect, the invention provides a transdermal patch for sustained transdermal administration of a pharmaceutical product having anti-anginal and platelet

washing properties to a patient in need of such properties comprising a backing, an adhesive for applying the patch, in which a pharmaceutical product having anti-anginal and platelet washing properties is incorporated in the adhesive on an amount sufficient to transdermally permeate the skin and achieve desired plasma levels.

The invention also provides the use of a pharmaceutical product having anti-anginal and platelet washing properties for preparing a transdermal patch comprising a backing, an adhesive for applying the patch, and a liner which is released to apply the patch, in which the pharmaceutical product is incorporated in the adhesive in an amount sufficient to transdermally permeate the skin and achieve desired plasma levels.

The invention further provides a method for achieving a platelet washing and anti-anginal effect in a patient comprising the step of applying a transdermal patch comprising a backing, an adhesive for applying the patch, and a liner which is released to apply the patch to the patient's skin, a pharmaceutical product having anti-anginal and platelet washing properties being incorporated in the adhesive in an amount sufficient to transdermally permeate the skin and achieve desired plasma levels.

In a particularly preferred embodiment of the invention the pharmaceutical product comprises a first pharmaceutical having antianginal properties and a second pharmaceutical having platelet washing properties.

Preferably the first pharmaceutical is Aspirin. Preferably the second pharmaceutical is an organic nitrate, especially a long acting nitrate. In a particularly preferred embodiment of the invention the nitrate is isosorbide mononitrate, especially isosorbide 2-

mononitrate or isosorbide-5-mononitrate. The nitrate may also be isosorbide dinitrate.

In a preferred embodiment of the invention the first pharmaceutical and the second pharmaceutical are incorporated into the adhesive. Preferably the adhesive is a pressure sensitive adhesive, based, for example, on acrylic acid copolymers.

In one embodiment of the invention, the adhesive is applied to the release liner. Typically, the release liner is a fluoro-polymeric-coated polyester.

Preferably, the backing comprises a backing layer attached to the adhesive. Alternatively, the liner is a siliconised release liner. Typically the backing layer comprises aluminised polyester. In one case the aluminised polyester is sputter coated onto the adhesive.

In another embodiment of the invention the patch includes a penetration enhancer to promote the diffusion of the pharmaceutically active product.

The invention also provides a method for producing a transdermal patch comprising the steps of incorporating a pharmaceutically active product having antianginal and platelet washing properties into an adhesive,

coating the adhesive onto a release liner, and

applying a backing layer.

According to another aspect, the invention provides a method for achieving an anti-anginal effect and for reducing platelet aggregation in a patient comprising the step of applying to a patient a transdermal patch of the

invention.

The purpose of the present invention is to provide a once daily treatment for the prophylaxis of angina in combination with an anti-platelet effect. To achieve this isosorbide mononitrate and aspirinate are delivered transdermally for up to a 24 hour period in an amount sufficient to provide therapeutic efficacy. Due to the comparatively long half-life of isosorbide mononitrate it may be preferable to leave the isosorbide mononitrate aspirinate transdermal patch in contact with skin for a period of time less than 24 hours. Although circulating concentrations of isosorbide mononitrate would decrease it is likely that there would be sufficient residual plasma levels of the compound to prevent pre-dose rebound due to the comparatively long half-life of isosorbide mononitrate.

The invention will be more clearly understood from the following description thereof given by way of example only with reference to the accompanying drawing which is a diagrammatic cross sectional view of a transdermal patch according to the invention.

Referring to the drawing, there is illustrated a transdermal patch according to the invention comprising a pressure sensitive adhesive layer (b) into which the pharmaceutically active product is incorporated, a release liner (c) and a backing (a).

The drug has been incorporated directly into a pressure-sensitive adhesive such as, but not limited to, acrylic acid copolymers (b). This mixture can then be cast, rolled or knife-coated onto a suitable release-liner such as, but not limited to, a fluoropolymeric-coated polyester (c). A backing-layer such as, but not limited to, a

sputter-coated aluminised polyester (to prevent drug strike though) can then be attached (a). The release-liner (c) is removed before the drug containing adhesive is presented to the skin. Unusually, this patch has been designed so that skin acts as the rate-determining membrane to drug diffusion. The advantage of this system is that this will provide the most efficient delivery of drug through the skin. This, in turn, will provide the smallest unit area of skin for drug delivery and hence the smallest patch size. This is an important consideration given the possible daily amounts of drug required by the transdermal route.

A further advantage of the invention is that aspirin can be delivered directly into the system thus avoiding first pass metabolism. Furthermore, delivering Aspirin transdermally will also prevent its known adverse side-effects on the gastrointestinal tract in some patients.

A further aspect of this invention is the use of various penetration enhancers to promote the diffusion of isosorbide mononitrate and aspirin through the skin to the systemic circulation. The advantage of this is in reducing the size (area) of the patch required to deliver a specific amount of the drugs to the systemic circulation. Examples of such penetration enhancers include, but is not limited to, propylene glycol, oleic acid, isopropyl myristate, dimethylsulphoxide, ethanol, and/or limonene.

A variety of suitable matrices may be used as a drug reservoir. These include the above mentioned acrylate co-polymers, polyisobutylenes and silicon-based adhesives. Other excipients present in the formulation may include plasticisers such as diethylphthalate, dibutylphthalate and/or glycerol.

Example 1

A transdermal system for isosorbide mononitrate and aspirin was prepared as follows. A pressure sensitive adhesive solution (PSA) was prepared using DURO-TAK 387-2054 dissolved in ethyl acetate. 108 mg of isosorbide mononitrate and 102 mg of aspirin were dissolved in 20 g of PSA and cast onto a siliconised polyester release liner using a 10 x 10 cm template. The film was oven dried after which an aluminium sputter-coated polyester backing layer was attached to the exposed, drug-containing, adhesive film (dry weight 5 g). Thereafter, 1 cm^2 sections were cut from the laminate and examined for drug release using silicone-based (Silescol) sheeting in a Franz cell (Fig. 2).

Patches (5 x 5 cm^2) were also applied to 5 human volunteers for a 24 hour period. Thereafter, the patches were removed and extracted for remaining ISMN and aspirin. It can be seen from Fig. 3 that, typically, 20 - 30% of ISMN had been absorbed from the patches within a 24 hour period and that, typically, 30 - 40% of aspirin had been absorbed from the patches within a 24 hour period.

DURO-TAK are a range of adhesives available from National Starch.

Silescol is manufactured by Esco Rubber and is available from Bibby Sterilin.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A transdermal patch comprising :-

a backing;

an adhesive for applying the patch; and

a liner which is released to apply the patch,

characterised in that

the adhesive contains a pharmaceutical product having anti-anginal and platelet washing properties.

2. A transdermal patch as claimed in claim 1 wherein the pharmaceutical product comprises a first pharmaceutical having antianginal properties and a second pharmaceutical having platelet washing properties.

3. A transdermal patch as claimed in claim 2 wherein the second pharmaceutical is Aspirin.

4. A transdermal patch as claimed in claim 2 or 3 wherein the first pharmaceutical is an organic nitrate.

5. A transdermal patch as claimed in claim 4 wherein the organic nitrate is a long acting nitrate.

6. A transdermal patch as claimed in claim 5 wherein the organic nitrate is isosorbide mononitrate.

7. A transdermal patch as claimed in claim 5 wherein the organic nitrate is isosorbide dinitrate.

8. A transdermal patch as claimed in claim 5 wherein the organic nitrate is isosorbide-2-nitrate.

9. A transdermal patch as claimed in claim 5 wherein the organic nitrate is isosorbide-5-nitrate.

10. A transdermal patch as claimed in any of claims 2 to 9 wherein the first pharmaceutical and the second pharmaceutical are incorporated into the adhesive.

11. A transdermal patch as claimed in any preceding claim wherein the adhesive is a pressure sensitive adhesive.

12. A transdermal patch as claimed in claim 11 wherein the adhesive is based on acrylic acid copolymers.

13. A transdermal patch as claimed in any preceding claim wherein the adhesive is applied to the release liner.

14. A transdermal patch as claimed in any preceding claim wherein the release liner is a fluoro-polymeric-coated polyester.

15. A transdermal patch as claimed in any of claims 1 to 14 wherein the liner is a siliconised release liner.

16. A transdermal patch as claimed in any preceding claim wherein the backing comprises a backing layer attached to the adhesive.

17. A transdermal patch as claimed in any preceding claim wherein the backing layer comprises aluminised polyester.

18. A transdermal patch as claimed in claim 17 wherein the aluminised polyester is sputter coated onto the adhesive.

19. A transdermal patch as claimed in any of claims 2 to 18 including a penetration enhancer to promote the diffusion of the first and/or second pharmaceutical.

20. A transdermal patch as claimed in claim 19 wherein the penetration enhancer is selected from one or more of propylene glycol, oleic acid, isopropyl myristate, dimethylsulphoxide, ethanol or limonene.

21. A transdermal patch substantially as hereinbefore described with reference to the example and drawings.

22. A method for producing a transdermal patch comprising the steps of incorporating a first pharmaceutical having antianginal properties and a second pharmaceutical having platelet washing properties into an adhesive; coating the adhesive onto a release liner; and applying a backing layer.

23. A method for producing a transdermal patch substantially as hereinbefore described with reference to the example and drawing.

24. A transdermal patch whenever produced by a method as claimed in claim 22 or 23.

25. A method for achieving an anti-anginal effect and for reducing platelet aggregation in a patient comprising the step of applying to a patient a transdermal patch as claimed in any of claims 1 to 21 or 24.

26. A method for achieving an anti-anginal effect and for reducing platelet aggregation in a patient substantially as hereinbefore described with reference to the examples and drawings.

27. A transdermal patch for sustained transdermal administration of a pharmaceutical product having anti-anginal and platelet washing properties to a patient in need of such properties comprising a backing, an adhesive for applying the patch, in which a pharmaceutical product having anti-anginal and platelet washing properties is incorporated in the adhesive on an amount sufficient to transdermally permeate the skin and achieve desired plasma levels.

28. Use of a pharmaceutical product having anti-anginal and platelet washing properties for preparing a transdermal patch comprising a backing, an adhesive for applying the patch, and a liner which is released to apply the patch, in which the pharmaceutical product is incorporated in the adhesive in an amount sufficient to transdermally permeate the skin and achieve desired plasma levels.

29. A method for achieving a platelet washing and anti-anginal effect in a patient comprising the step of applying a transdermal patch comprising a backing, an adhesive for applying the patch, and a liner which is released to apply the patch to the patient's skin, a pharmaceutical product having anti-anginal and platelet washing properties being incorporated in the adhesive in an amount sufficient to transdermally permeate the skin and achieve desired plasma levels.

1/2 (FORMAL)

FIG. 1

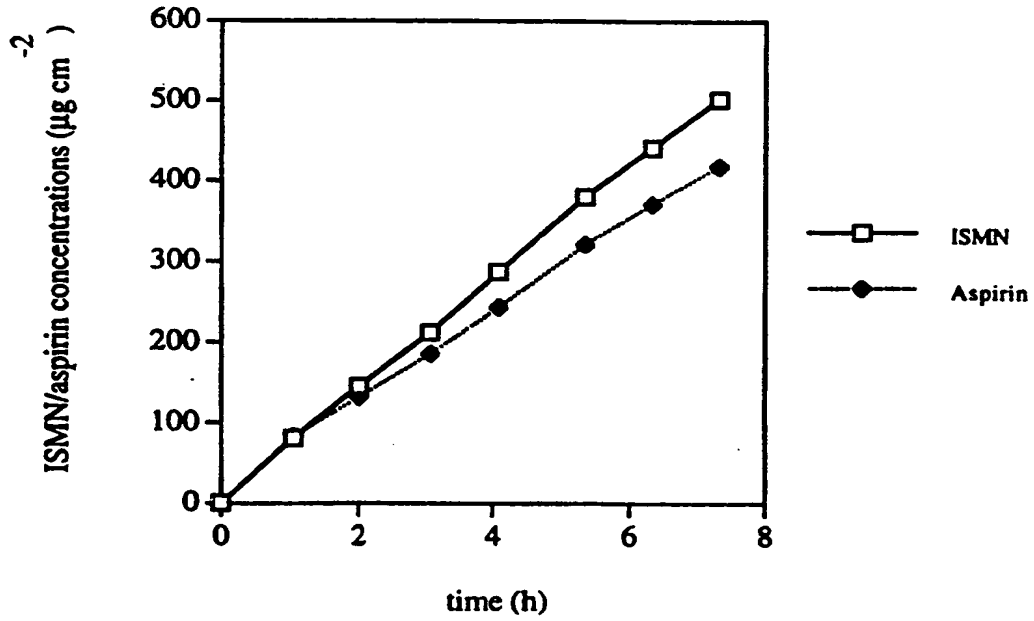

Fig. 2 Penetration of ISMN and aspirin through Silescol

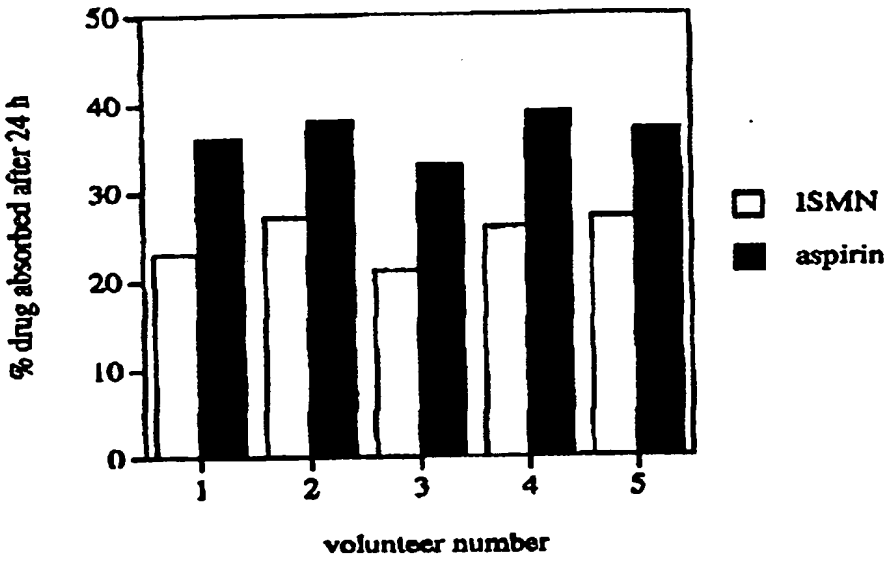

Fig. 3 % ISMN and aspirin absorbed, in vivo, after 24 h

INTERNATIONAL SEARCH REPORT

Internati · Application No
PCT/IE 96/00048

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 03421 (CAL INTERNATIONAL LIMITED) 17 February 1994 see the whole document ---	1-29
A	DE,A,42 41 128 (LTS LOHMANN THERAPIE-SYSTEMEN) 24 June 1993 see the whole document -----	1-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
16 January 1997	24. 01. 97

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IE 96/00048

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 25, 26 and 29 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Interna... ...l Application No
PCT/IE 96/00048

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9403421	17-02-94	AU-A-	1225795	04-05-95
		AU-B-	673846	28-11-96
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		NZ-A-	246158	26-10-95
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